

WHAT IS CLAIMED IS:

- 1 1. A method for reducing pain in a subject in need thereof by
2 increasing ion flow through KCNQ potassium channels in a cell, the method comprising
3 the step of administering to the subject a pharmaceutical composition comprising a
4 pharmaceutically acceptable carrier and a compound able to increase ion flow through
5 KCNQ potassium channels, said composition administered to the subject in a potassium
6 channel-opening amount, thereby reducing pain in the subject.
- 1 2. The method of claim 1, wherein the pain is somatic pain.
- 1 3. The method of claim 2, wherein the pain is cutaneous.
- 1 4. The method of claim 2, wherein the pain is visceral.
- 1 5. The method of claim 2, wherein the pain is caused by a burn, a
2 bruise, an abrasion, a laceration, a broken bone, a torn ligament, a torn tendon, a torn
3 muscle, a viral infection, a bacterial infection, a protozoal infection, a fungal infection,
4 contact dermatitis, inflammation, or cancer.
- 1 6. The method of claim 5, wherein the inflammation is caused by
2 trauma, infection, surgery, burns, or diseases with an inflammatory component.
- 1 7. The method of claim 1, wherein the pain is neuropathic.
- 1 8. The method of claim 7, wherein the neuropathic pain is caused by
2 injury to the central or peripheral nervous system due to cancer, HIV infection, tissue
3 trauma, infection, autoimmune disease, diabetes, arthritis, diabetic neuropathy, trigeminal
4 neuralgia or drug administration.
- 1 9. The method of claim 1, wherein the subject is a human.
- 1 10. The method of claim 1, wherein the KCNQ channel is a
2 heteromeric channel.
- 1 11. The method of claim 1, wherein the KCNQ channel is a
2 homomeric channel.

1 12. The method of claim 10, wherein the heteromeric KCNQ channel
2 comprises a KCNQ2 polypeptide subunit.

1 13. The method of claim 10, wherein the heteromeric KCNQ channel
2 comprises a KCNQ3 polypeptide subunit.

1 14. The method of claim 12, wherein the KCNQ channel is KCNQ2/3.

1 15. The method of claim 1, wherein the potassium channel-opening
2 amount is 0.1 mg/kg to 200 mg/kg.

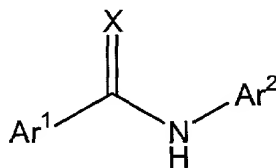
1 16. The method of claim 15, wherein the potassium channel-opening
2 amount is 10 mg/kg to 100 mg/kg.

1 17. The method of claim 1, wherein the composition is administered
2 orally.

1 18. The method of claim 1, wherein the composition is administered by
2 injection.

1 19. The method of claim 1, wherein the composition is administered
2 after a surgical procedure.

1 20. The method of claim 1, wherein the compound able to increase ion
2 flow through KCNQ potassium channels has the formula:



3
4 wherein

5 Ar¹ and Ar² are each members independently selected from the group
6 consisting of aryl, substituted aryl, heteroaryl and substituted
7 heteroaryl; and

8 X is a member selected from the group consisting of O, S and N-R¹,
9 wherein R¹ is a member selected from the group consisting of H, (C₁-
10 C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl, heteroaryl,

11 substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted aryl(C₁-
12 C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, and -S(O)₂NR³R⁴;
13 wherein R² is a member selected from the group consisting of (C₁-
14 C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
15 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and
16 substituted aryl(C₁-C₄)alkyl; and
17 R³ and R⁴ are each members independently selected from the group
18 consisting of hydrogen, (C₁-C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl,
19 heteroaryl, substituted heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl, or R³
20 and R⁴ can be combined with the nitrogen to which each is attached to form a 5-, 6- or 7-
21 membered ring optionally having additional heteroatoms at the ring vertices.

1 21. The method according to claim 20, wherein Ar¹ is a member
2 selected from the group consisting of phenyl, substituted phenyl, indolyl, substituted
3 indolyl, benzofuranyl, substituted benzofuranyl, furanyl, substituted furanyl, thienyl,
4 substituted thienyl, isothiazolyl, substituted isothiazolyl, pyrazolyl and substituted
5 pyrazolyl.

1 22. The method according to claim 20, wherein Ar¹ is substituted
2 phenyl, substituted or unsubstituted 2-indolyl and substituted or unsubstituted 2-thienyl.

1 23. The method according to claim 20, wherein X is O.

1 24. The method according to claim 22, wherein the Ar¹ substituents are
2 selected from the group consisting of halogen, alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy,
3 halo(C₁-C₄)alkoxy, nitro, cyano, -NHC(O)R⁷, -NHR⁷, phenyl and substituted phenyl,
4 wherein
5 R⁷ is a member selected from hydrogen, (C₁-C₈)alkyl, substituted
6 (C₁-C₈)alkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl,
7 heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted
8 heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-C₄)alkyl, or R⁷ can be combined with
9 the nitrogen to which it is attached to form a 5-, 6- or 7-membered ring optionally having
10 additional heteroatoms at the ring vertices.

1 25. The method according to claim 20, wherein Ar² is selected from
2 the group consisting of heteroaryl and substituted heteroaryl.

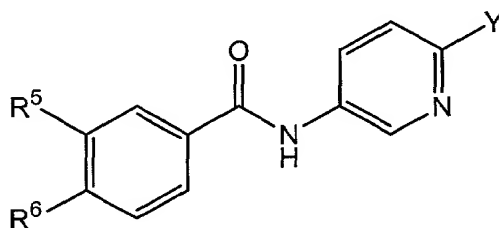
1 26. The method according to claim 20, wherein Ar¹ is substituted aryl;
2 Ar² is heteroaryl or substituted heteroaryl; and X is O.

1 27. The method according to claim 24, wherein Ar² is pyridyl or
2 substituted pyridyl.

1 28. The method according to claim 27, wherein Ar² is selected from
2 the group consisting of 6-methyl-3-pyridyl and 2-chloro-5-pyridyl.

1 29. The method according to claim 27, wherein Ar¹ is substituted
2 phenyl.

1 30. The method according to claim 29, said compound having the
2 formula:

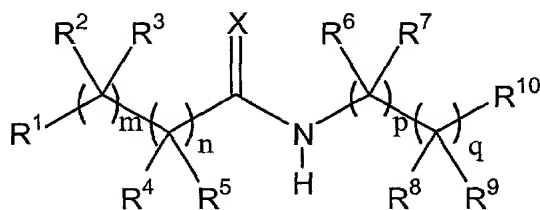


3
4 wherein,

5 Y is a member selected from the group consisting of halogen, C₁-C₄ alkyl,
6 C₁-C₄ substituted alkyl, -OCH₃ and -OCF₃, and R⁵ and R⁶ are members independently
7 selected from the group consisting of H, halogen, alkyl, halo(C₁-C₄)alkyl, nitro, cyano
8 and phenyl, with the proviso that both R⁵ and R⁶ are not H.

1 31. The method according to claim 30, wherein R⁵ and R⁶ are members
2 independently selected from the group consisting of H, F, and Cl, with the proviso that
3 both R⁵ and R⁶ are not H.

1 32. The method of claim 1, wherein the compound able to increase ion
2 flow through KCNQ potassium channels has the formula:



wherein

R^1 is a member selected from the group consisting of substituted or unsubstituted branched (C_3 - C_8)alkyl, substituted or unsubstituted (C_3 - C_8)cycloalkyl, substituted or unsubstituted (C_3 - C_8)heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^2 , R^3 , R^4 and R^5 are each members independently selected from the group consisting of hydrogen, fluorine and substituted or unsubstituted (C_1 - C_8)alkyl, or optionally any two of R^2 , R^3 , R^4 and R^5 are joined together to form a three- to seven-membered ring, having from 0 to 3 heteroatoms as ring members, or R^2 and R^4 taken together form a second bond between the carbon atoms to which each is attached, or R^2 , R^3 , R^4 and R^5 taken together represent a second and third bond between the carbon atoms to which each is attached;

R^6 , R^7 , R^8 and R^9 are each members independently selected from the group consisting of hydrogen, fluorine and substituted or unsubstituted (C_1 - C_8)alkyl, or optionally any two of R^6 , R^7 , R^8 and R^9 are joined together to form a three- to seven-membered ring, having from 0 to 3 heteroatoms as ring members;

R^{10} is a member selected from the group consisting of substituted or unsubstituted (C_3 - C_8)cycloalkyl, substituted or unsubstituted (C_3 - C_8)heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

X is a member selected from the group consisting of O, S and $N-R^{11}$, wherein R^{11} is a member selected from the group consisting of H, (C_1 - C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl, substituted aryl(C_1 - C_4)alkyl, -CN, -C(O) R^{12} , -OR¹³, -NR¹³R¹⁴, -C(O)NR¹³R¹⁴, and -S(O)₂NR¹³R¹⁴;

wherein R^{12} is a member selected from the group consisting of (C_1 - C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl and substituted aryl(C_1 - C_4)alkyl; and

37 R^{13} and R^{14} are each members independently selected from the
38 group consisting of hydrogen, (C₁-C₈)alkyl, substituted (C₁-
39 C₈)alkyl, aryl, substituted aryl, heteroaryl, substituted
40 heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-
41 C₄)alkyl, or R^{13} and R^{14} can be combined with the nitrogen
42 to which each is attached to form a 5-, 6- or 7-membered
43 ring optionally having additional heteroatoms at the ring
44 vertices; and

45 m, n, p and q are each independently an integer of from 0 to 1, with the
46 proviso that at least one of m, n, p or q is 1.

1 33. The method of claim 32, wherein X of the compound is O.

1 34. The method of claim 32, wherein m and n of the compound are
2 zero.

1 35. The method of claim 32, wherein m of the compound is 1 and n of
2 the compound is zero.

1 36. The method of claim 32, wherein m and n of the compound are
2 each 1.

1 37. The method of claim 32, wherein m and p of the compound are
2 each zero, and n and q of the compound are each 1.

1 38. The method of claim 32, wherein m, n, p and q of the compound
2 are each 1.

1 39. The method of claim 32, wherein R^2 and R^4 of the compound,
2 taken together, form a second bond joining the carbon atoms to which each is attached.

1 40. The method of claim 32, wherein m and p of the compound are
2 each 1, R^2 , R^3 , R^6 and R^7 of the compound are each hydrogen, n and q of the compound
3 are each zero, and R^{10} of the compound is selected from the group consisting of
4 substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

1 41. The method of claim 40, wherein R¹⁰ of the compound is
2 substituted aryl having from one to three substituents selected from the group consisting
3 of halogen, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, nitro,
4 cyano, phenyl and methylenedioxy.

1 42. The method of claim 32, wherein m, n, p and q of the compound
2 are each 1, and R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ of the compound are each hydrogen.

1 43. The method of claim 32, wherein m, n, p and q of the compound
2 are each 1; R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ of the compound are each hydrogen; and R¹⁰
3 of the compound is selected from the group consisting of substituted or unsubstituted aryl
4 and substituted or unsubstituted heteroaryl.

1 44. The method of claim 43, wherein R¹ of the compound is selected
2 from the group consisting of substituted or unsubstituted branched (C₃-C₈)alkyl, and
3 substituted or unsubstituted (C₃-C₈)cycloalkyl.

1 45. A method for reducing anxiety in a subject in need thereof by
2 increasing ion flow through KCNQ potassium channels in a cell, the method comprising
3 the step of administering to the subject a pharmaceutical composition comprising a
4 pharmaceutically acceptable carrier and a compound able to increase ion flow through
5 KCNQ potassium channels, said composition administered to the subject in a potassium
6 channel-opening amount, thereby reducing anxiety in the subject.

1 46. The method of claim 45, wherein the anxiety is caused by panic
2 disorder, generalized anxiety disorder, or stress disorder.

1 47. The method of claim 46, wherein the stress disorder is acute stress
2 disorder or post-traumatic stress disorder.

1 48. The method of claim 45, wherein the subject is a human.

1 49. The method of claim 45, wherein the KCNQ channel is a
2 heteromeric channel.

1 50. The method of claim 45, wherein the KCNQ channel is a
2 homomeric channel.

1 51. The method of claim 50, wherein the heteromeric KCNQ channel
2 comprises a KCNQ2 polypeptide subunit.

1 52. The method of claim 50, wherein the heteromeric KCNQ channel
2 comprises a KCNQ3 polypeptide subunit.

1 53. The method of claim 52, wherein the KCNQ channel is KCNQ2/3.

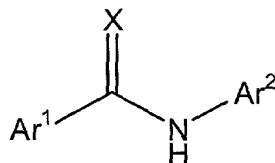
1 54. The method of claim 45, wherein the potassium channel-opening
2 amount is 0.1 mg/kg to 200 mg/kg.

1 55. The method of claim 54, wherein the potassium channel-opening
2 amount is 10 mg/kg to 100 mg/kg.

1 56. The method of claim 45, wherein the composition is administered
2 orally.

1 57. The method of claim 45, wherein the composition is administered
2 by injection.

1 58. The method of claim 45, wherein the compound able to increase
2 ion flow through KCNQ potassium channels has the formula:



4 wherein

5 Ar¹ and Ar² are each members independently selected from the group
6 consisting of aryl, substituted aryl, heteroaryl and substituted
7 heteroaryl; and

8 X is a member selected from the group consisting of O, S and N-R¹,
9 wherein R¹ is a member selected from the group consisting of H, (C₁-
10 C₈)alkyl, substituted (C₁-C₈)alkyl, aryl, substituted aryl, heteroaryl,
11 substituted heteroaryl, aryl(C₁-C₄)alkyl, substituted aryl(C₁-
12 C₄)alkyl, CN, -C(O)R², -OR³, -C(O)NR³R⁴, and -S(O)₂NR³R⁴;

13 wherein R^2 is a member selected from the group consisting of (C_1 -
14 C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl,
15 heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl and
16 substituted aryl(C_1 - C_4)alkyl; and
17 R^3 and R^4 are each members independently selected from the group
18 consisting of hydrogen, (C_1 - C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl,
19 heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl and substituted aryl(C_1 - C_4)alkyl, or R^3
20 and R^4 can be combined with the nitrogen to which each is attached to form a 5-, 6- or 7-
21 membered ring optionally having additional heteroatoms at the ring vertices.

1 59. The method according to claim 58, wherein Ar^1 is a member
2 selected from the group consisting of phenyl, substituted phenyl, indolyl, substituted
3 indolyl, benzofuranyl, substituted benzofuranyl, furanyl, substituted furanyl, thienyl,
4 substituted thienyl, isothiazolyl, substituted isothiazolyl, pyrazolyl and substituted
5 pyrazolyl.

1 60. The method according to claim 58, wherein Ar^1 is substituted
2 phenyl, substituted or unsubstituted 2-indolyl and substituted or unsubstituted 2-thienyl.

1 61. The method according to claim 58, wherein X is O.

1 62. The method according to claim 60, wherein the Ar^1 substituents are
2 selected from the group consisting of halogen, alkyl, halo(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy,
3 halo(C_1 - C_4)alkoxy, nitro, cyano, $-NHC(O)R^7$, $-NHR^7$, phenyl and substituted phenyl,
4 wherein

5 R^7 is a member selected from hydrogen, (C_1 - C_8)alkyl, substituted
6 (C_1 - C_8)alkyl, cycloalkyl, substituted cycloalkyl, heteroalkyl, substituted heteroalkyl,
7 heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted
8 heteroaryl, aryl(C_1 - C_4)alkyl and substituted aryl(C_1 - C_4)alkyl, or R^7 can be combined with
9 the nitrogen to which it is attached to form a 5-, 6- or 7-membered ring optionally having
10 additional heteroatoms at the ring vertices.

1 63. The method according to claim 58, wherein Ar^2 is selected from
2 the group consisting of heteroaryl and substituted heteroaryl.

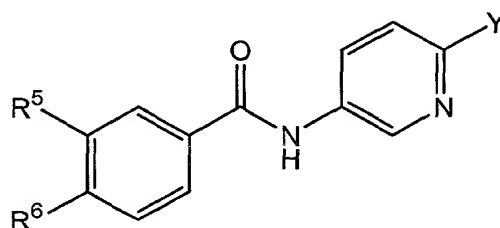
1 64. The method according to claim 58, wherein Ar¹ is substituted aryl;
2 Ar² is heteroaryl or substituted heteroaryl; and X is O.

1 65. The method according to claim 62, wherein Ar² is pyridyl or
2 substituted pyridyl.

1 66. The method according to claim 65, wherein Ar² is selected from
2 the group consisting of 6-methyl-3-pyridyl and 2-chloro-5-pyridyl.

1 67. The method according to claim 65, wherein Ar¹ is substituted
2 phenyl.

1 68. The method according to claim 67, said compound having the
2 formula:

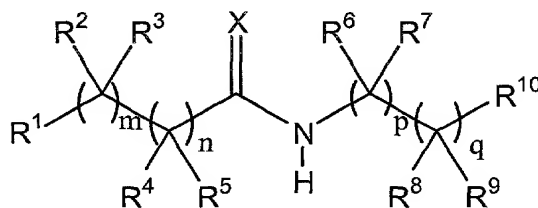


3
4 wherein,

5 Y is a member selected from the group consisting of halogen, C₁-C₄ alkyl,
6 C₁-C₄ substituted alkyl, -OCH₃ and -OCF₃, and R⁵ and R⁶ are members independently
7 selected from the group consisting of H, halogen, alkyl, halo(C₁-C₄)alkyl, nitro, cyano
8 and phenyl, with the proviso that both R⁵ and R⁶ are not H.

1 69. The method according to claim 68, wherein R⁵ and R⁶ are members
2 independently selected from the group consisting of H, F, and Cl, with the proviso that
3 both R⁵ and R⁶ are not H.

1 70. The method of claim 45, wherein the compound able to increase
2 ion flow through KCNQ potassium channels has the formula:



wherein

R^1 is a member selected from the group consisting of substituted or unsubstituted branched (C_3 - C_8)alkyl, substituted or unsubstituted (C_3 - C_8)cycloalkyl, substituted or unsubstituted (C_3 - C_8)heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^2 , R^3 , R^4 and R^5 are each members independently selected from the group consisting of hydrogen, fluorine and substituted or unsubstituted (C_1 - C_8)alkyl, or optionally any two of R^2 , R^3 , R^4 and R^5 are joined together to form a three- to seven-membered ring, having from 0 to 3 heteroatoms as ring members, or R^2 and R^4 taken together form a second bond between the carbon atoms to which each is attached, or R^2 , R^3 , R^4 and R^5 taken together represent a second and third bond between the carbon atoms to which each is attached;

R^6 , R^7 , R^8 and R^9 are each members independently selected from the group consisting of hydrogen, fluorine and substituted or unsubstituted (C_1 - C_8)alkyl, or optionally any two of R^6 , R^7 , R^8 and R^9 are joined together to form a three- to seven-membered ring, having from 0 to 3 heteroatoms as ring members;

R^{10} is a member selected from the group consisting of substituted or unsubstituted (C_3 - C_8)cycloalkyl, substituted or unsubstituted (C_3 - C_8)heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

X is a member selected from the group consisting of O, S and $N-R^{11}$, wherein R^{11} is a member selected from the group consisting of H, (C_1 - C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl, substituted aryl(C_1 - C_4)alkyl, -CN, -C(O) R^{12} , -OR¹³, -NR¹³ R^{14} , -C(O)NR¹³ R^{14} , and -S(O)₂NR¹³ R^{14} ;

wherein R^{12} is a member selected from the group consisting of (C_1 - C_8)alkyl, substituted (C_1 - C_8)alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryl(C_1 - C_4)alkyl and substituted aryl(C_1 - C_4)alkyl; and

37 R^{13} and R^{14} are each members independently selected from the
38 group consisting of hydrogen, (C₁-C₈)alkyl, substituted (C₁-
39 C₈)alkyl, aryl, substituted aryl, heteroaryl, substituted
40 heteroaryl, aryl(C₁-C₄)alkyl and substituted aryl(C₁-
41 C₄)alkyl, or R^{13} and R^{14} can be combined with the nitrogen
42 to which each is attached to form a 5-, 6- or 7-membered
43 ring optionally having additional heteroatoms at the ring
44 vertices; and

45 m, n, p and q are each independently an integer of from 0 to 1, with the
46 proviso that at least one of m, n, p or q is 1.

1 71. The method of claim 70, wherein X of the compound is O.

1 72. The method of claim 70, wherein m and n of the compound are
2 zero.

1 73. The method of claim 70, wherein m of the compound is 1 and n of
2 the compound is zero.

1 74. The method of claim 70, wherein m and n of the compound are
2 each 1.

1 75. The method of claim 70, wherein m and p of the compound are
2 each zero, and n and q of the compound are each 1.

1 76. The method of claim 70, wherein m, n, p and q of the compound
2 are each 1.

1 77. The method of claim 70, wherein R^2 and R^4 of the compound,
2 taken together, form a second bond joining the carbon atoms to which each is attached.

1 78. The method of claim 70, wherein m and p of the compound are
2 each 1, R^2 , R^3 , R^6 and R^7 of the compound are each hydrogen, n and q of the compound
3 are each zero, and R^{10} of the compound is selected from the group consisting of
4 substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

1 79. The method of claim 78, wherein R^{10} of the compound is
2 substituted aryl having from one to three substituents selected from the group consisting
3 of halogen, halo(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, nitro,
4 cyano, phenyl and methylenedioxy.

1 80. The method of claim 70, wherein m, n, p and q of the compound
2 are each 1, and R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 of the compound are each hydrogen.

1 81. The method of claim 70, wherein m, n, p and q of the compound
2 are each 1; R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 of the compound are each hydrogen; and R^{10}
3 of the compound is selected from the group consisting of substituted or unsubstituted aryl
4 and substituted or unsubstituted heteroaryl.

1 82. The method of claim 81, wherein R^1 of the compound is selected
2 from the group consisting of substituted or unsubstituted branched (C₃-C₈)alkyl, and
3 substituted or unsubstituted (C₃-C₈)cycloalkyl.